Journal of Surgical Oncology 1999;70:71–77

30 Gy May Be an Adequate Dose in Patients With Anal Cancer Treated With Excisional Biopsy Followed by Combined-Modality Therapy

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Background and Objectives: There are a subset of patients with invasive anal cancers who undergo an excisional biopsy either before or after combined-modality therapy (CMT). The objective of this study is to determine whether these patients can be adequately treated with a lower dose of pelvic radiation therapy.

Methods: A total of 25 patients were treated with CMT either before or after an excisional biopsy. The four subsets included 8 patients with initial excision followed by CMT with 30–34 Gy (EX/30), 6 patients with initial excision followed by CMT with 45–50.4 Gy (EX/45), 10 patients treated by CMT with 30 Gy followed by an excision (30/EX), and 1 patient by CMT with 45 Gy followed by an excision (45/EX).

Results: For the total group, the actuarial 5-year disease-free survival was 78%, overall survival was 86%, colostomy-free survival was 91%, and local control was 82%. When patients received CMT either before or following an excision, the actuarial local control and survival results with 30–34 Gy vs. 45–50.4 Gy were similar. In contrast to radiation dose, in patients who received 30–34 Gy, the sequence of the excision (before or after CMT) did appear to have a borderline significant impact on local control. Actuarial 5-year local control was 100% for EX/30 vs. 67% for 30/EX ($P = 0.08$).

Conclusions: Because of the small number of patients in each group and the retrospective nature of the analysis, it is difficult to draw definitive conclusions from this study. However, our data suggest that in patients who are selected to undergo an initial excisional biopsy followed by CMT, 30 Gy may be an adequate radiation dose. Local control may be higher in patients who undergo an excisional biopsy followed by CMT compared with the converse. *J. Surg. Oncol. 1999;70:71–77.*

KEY WORDS: anal cancer; combined-modality therapy; radiation therapy

INTRODUCTION

The treatment of invasive squamous cell carcinoma of the anal canal has evolved from an abdominoperineal

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Accepted 17 November 1998

TABLE I. Anal Cancer Patient and Tumor Characteristics*

	EX/30	EX/45	30/EX	45/EX
Number of patients	8	6	10	1
Treatment	Excisional biopsy then posteroperative 3,000–3,400 cGy	Excisional biopsy then postoperative 4,500 cGy	Preoperative 3,000 cGy then excisional biopsy	Preoperative 4,500 cGy then excisional biopsy
Median age	60	55	66	72
Male:female	1:1	1:5	1:2.3	1:0
Tumor size (average), cm	2.3	2.8	1.8	5
Margin positive	2 (25%)	2 (33%)	0	0
Stage IIIA/B	2 (25%)	0	2 (20%)	0
Adenocarcinoma	1 (13%)	1 (17%)	1 (10%)	0
Median follow-up (months)	81	42	80	113
Sequential therapy	3 (38%)	2 (33%)	7 (70%)	1/1

*EX/30 = initial excisional biopsy followed by 30 Gy; EX/45 = initial excisional biopsy followed by 45 Gy; 30/EX = 30 Gy followed by excisional biopsy; 45/EX = 45 Gy followed by excisional biopsy.

resection to one based on a nonoperative combined-modality therapy approach. Prior to the mid-1970s, abdominoperineal resection remained the standard of care, yielding 5-year overall survival rates of 35%–69% [1–4]. Following the preliminary report by Nigro et al. [1] of pathologic complete responses following 30 Gy plus 5-fluorouracil (5-FU) and mitomycin-C, the nonoperative approach has become the standard of care. At the present time, the most common approach, as developed by the Radiation Therapy Oncology Group (RTOG), is 30-Gy whole pelvis followed by 15 Gy to the true pelvis. This is combined with two cycles of concurrent continuous infusion 5-FU and bolus mitomycin-C. In most series, 5-year overall and colostomy-free survival with combined-modality therapy have ranges of 65%–90% [6–9] and 80%–90% [8,10], respectively.

The most common role of surgery in this disease is an incisional biopsy for diagnosis or salvage abdominoperineal resection for patients with local failure. However, there are a subset of patients with invasive cancers who, for a variety of reasons, undergo an excisional biopsy such as a hemorrhoidectomy, polypectomy, or local excision either before or after combined-modality therapy. Since the margins may be either negative or at most microscopically positive, is full-dose radiation (45 Gy) required or are lower doses of radiation equally as effective? The purpose of this study is to determine whether patients who undergo an excisional biopsy either before or after combined-modality therapy can be adequately treated with a lower dose of radiation.

MATERIALS AND METHODS

The records of 149 patients treated for invasive carcinoma of the anal canal at Memorial Sloan-Kettering Cancer Center between 1980 and 1995 were reviewed retrospectively. Of these, 25 (12 male, 13 female) were referred to the Department of Radiation Oncology either before or following an excisional biopsy and were treated with combined-modality therapy. The median age was 62 years and the median follow-up was 74 months (range, 1–161 months). The median primary tumor size was 3 cm (range, 0.5–5 cm). Of the 25 patients, 22 had squamous-cell carcinoma and 3 had adenocarcinoma. Clinical stage according to the American Joint Committee TNM staging system [11] included stage I: 10; stage II: 10; stage IIIA: 3; and stage IIIB: 2.

The sequence of treatment was dependent on physician preference and, since the study period included patients treated over 15 years, there were a range of approaches. All patients received combined-modality therapy. The four subsets of patents are as follows. One, eight patients underwent an initial excisional biopsy then received combined-modality therapy with 30–34 Gy and were designated ''EX/30.'' Two, six patients underwent an initial excisional biopsy and then received combined-modality therapy except the dose of radiation was 45–50.4 Gy. This group was designated ''EX/45.'' Three, 10 patients initially received combined-modality therapy with 30 Gy then underwent an excisional biopsy and were designated as ''30/EX.'' Four, one patient initially received combined-modality therapy with 45 Gy and then underwent an excisional biopsy and was designated ''45/EX.'' Patient and tumor characteristics for the four subsets are listed in Table I. The five patients with advanced stages of disease (stages IIIA/B) were treated in groups EX/30 or 30/EX and received 30–34 Gy.

Surgery

Of the 25 patients, 23 underwent an excisional biopsy (3 hemorrhoidectomies and 22 local excisions) at Memorial Sloan-Kettering Cancer Center. Two underwent an excisional biopsy at an outside institution. All of the patients who underwent an excisional biopsy following combined-modality therapy had negative margins,

whereas 4 of the 14 (29%) who underwent a excisional biopsy prior to combined-modality therapy had microscopic positive margins. Margin status was not a factor in determining subsequent radiation treatment dose.

Of the three patients who presented with pathologically positive inguinal lymph nodes, one underwent an inguinal lymph node dissection following combined-modality therapy. The other two patients had an excisional biopsy only followed by combined-modality therapy.

Three patients underwent a salvage abdominoperineal resection. It was performed for local-only failure in two patients and both local and distant failure in one patient.

Radiation Therapy

In general, prior to 1986, pelvic radiation therapy was performed anteroposterior/posteroanterior (AP/PA) with at least 6-Mv photons. The whole pelvis plus inguinal nodes received 2 Gy/day prescribed to a point.

In 1986, the treatment policy at Memorial Sloan-Kettering was revised and most patients received a three-field (PA and two laterals) with ⩾10 Mv at 1.8 Gy/day using a previously described technique [12]. Treatment planning was performed with computerized dosimetry and the dose was prescribed to the isodose line (95%–100%), which surrounded the treatment volume at risk. The whole pelvis received 30.6 Gy and some received a boost of 14.4 Gy to the true pelvis to a total dose of 45 Gy. Two patients received an additional boost (initial primary tumor plus margin) to 50.4 Gy. The inguinal nodes were included in the radiation field in all patients and treatment was supplemented with electrons to bring the total dose to the same as that for the primary tumor.

Overall, 17 of 18 patients in the 30–34-Gy group received 30 Gy. The dose was increased to 34 Gy in one patient who resumed treatment following a 2-week break for acute grade 3+ skin toxicity. Seven patients received 45–50.4 Gy.

Chemotherapy

The majority of patients were treated with a 4–5-day continuous infusion of 5-FU (median, 750 mg/m^2; range, 500–1,000 mg/m^2) and bolus mitomycin-C of 10–15 mg/m^2 the first day of each 5-FU infusion. Overall, 13 patients received sequential therapy (cycle 1 of chemotherapy began week 1 and radiation week 2), while 11 received concurrent therapy (both chemotherapy and radiation began week 1).

In the 14 patients who underwent an initial excisional biopsy followed by combined-modality therapy (EX/30 and EX/45), 9 (64%) received concurrent therapy and 5 (36%) received sequential therapy. In the 11 patients who underwent initial combined-modality therapy followed by an excisional biopsy (30/EX and 45/EX), 2 (18%) received concurrent therapy and 9 (82%) received sequential therapy

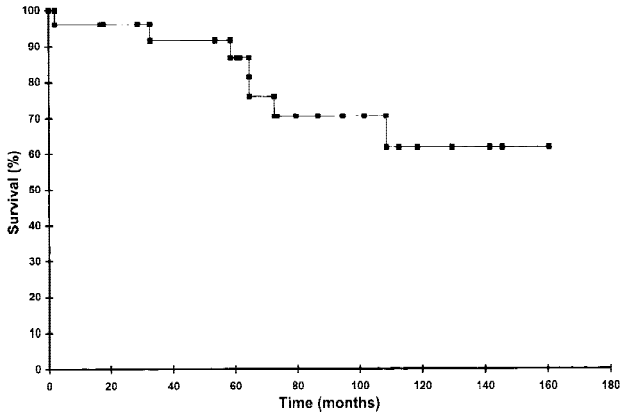

Fig. 1. Anal cancer: actuarial survival for the total patient group.

Sphincter Function

Sphincter function was assessed by a telephone evaluation and scored according to the Memorial Sloan-Kettering Anal Sphincter Function Criteria [13]: excellent denotes 1–2 bowel movements/day, no soilage; good, 3–4 bowel movements/day and/or mild soilage; fair, episodic >4 bowel movements/day and/or moderate soilage; poor, incontinence. The three patients who underwent a salvage abdominoperineal resection were excluded from sphincter function analysis.

Determination of Patterns of Failure

Failure sites were determined by clinical examination, X-ray, or biopsy. None were determined by autopsy or by reoperation in asymptomatic patients. Local control was expressed as the crude as well as actuarial incidence of cumulative (total) local control. Failure in the external beam pelvic field (tumor bed, pelvic, or inguinal nodes) was scored as local failure. Abdominal failure was defined as failure in the liver, retroperitoneal nodes, or by the presence of peritoneal seeding. Distant failure included lung, bone, or brain.

Statistical Analysis

Differences between crude proportions were analyzed by the chi-square test. Analysis of the actuarial patterns of failure and survival was performed using the Kaplan-Meier method and differences between actuarial proportions were analyzed by the log-rank test [14]. There were no treatment-related deaths. Patients were censored at last follow-up or if dead of other disease. The results were calculated from the completion of radiation therapy.

RESULTS

For the total group of 25 patients, the actuarial 5-year disease-free survival was 78% and, as seen in Figure 1,

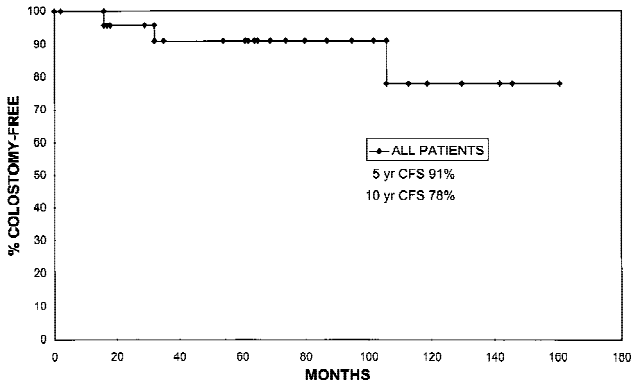

Fig. 2. Anal cancer: actuarial colostomy-free survival for the total patient group. CFS: colostomy-free survival

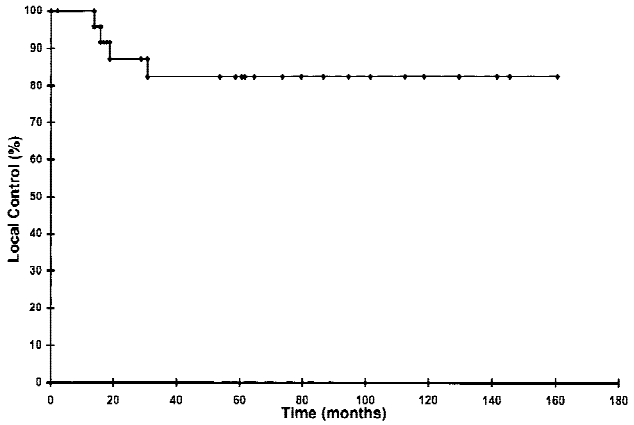

Fig. 3. Anal cancer: actuarial local control for the total patient group.

the overall survival was 86%. The actuarial colostomy-free survival was 91% at 5 years but decreased to 78% at 10 years (Fig. 2). The 5-year actuarial local control rate was 82% (Fig. 3) and the overall crude local control rate was 84% (21/25).

Impact of Radiation Dose on Local Control and Survival

In the 14 patients who underwent an initial excisional biopsy followed by combined-modality therapy (EX/30 plus EX/45), both the crude and 5-year actuarial local control rate was 93%. Only one of the six EX/45 patients recurred locally resulting in a 83% crude and 83% 5-year actuarial local control rate and all eight of the EX/30 patients (100%) were locally controlled ($P = 0.25$). The actuarial 5-year disease-free survival for the EX/30 group was 87% vs. 83% for the EX/45 group ($P = 0.92$), and the actuarial 5-year overall survival was 88% vs. 100%, respectively ($P = 0.56$). Crude survival rates were 88% (7/8) and 83% (5/6), respectively. These data suggest that when patients receive combined-modality therapy following an excisional biopsy, the results with doses of 30–34 Gy and 45 Gy are similar.

Similarly, for the 18 patients treated with 30–34 Gy who had the excisional biopsy performed either before or after combined-modality therapy (EX/30 plus 30/EX), the local control and survival results were not significantly different when compared with the 7 patients who received 45–50.4 Gy and had the excisional biopsy performed either before or after combined-modality therapy (EX/45 plus 45/EX). The 5-year actuarial local control, disease-free survival, and overall survival rates for the patients who received 30–34 Gy compared with those who received 45–50.4 Gy were 82% vs. 86%, 76% vs. 86%, and 83% vs. 100%, respectively (P = NS). The crude local control, disease-free survival, and overall survival rates were 83% vs. 86%, 72% vs. 85%, and 67% vs. 86%, respectively (P = NS).

Impact of the Sequence of Excisional Biopsy and Combined-Modality Therapy

In contrast to the radiation dose, the sequence of the excisional biopsy (before or after combined-modality therapy) did have a borderline significant impact on local control. Patients who underwent combined-modality therapy followed by an excisional biopsy had a less favorable local control rate compared to those undergoing an initial excisional biopsy followed by combined-modality therapy. As seen in Figure 4, the 10 patients who underwent combined-modality therapy with 30–34 Gy followed by an excisional biopsy (30/EX) had a lower actuarial 5-year local control rate compared with the 8 undergoing an initial excisional biopsy followed by combined-modality therapy with 30–34 cGy (EX/30) (67% vs. 100%, $P = 0.08$). The crude local control rates were 70% (7/10) and 100% (8/8), respectively.

Although the local control rates were lower, there was no significant impact on overall survival. The actuarial 5-year overall survival rates were 80% for 30/EX and 88% for EX/30 ($P = 0.25$), and the corresponding crude survival rates were 50% (5/10) and 88% (7/8), respectively (P = NS). The actuarial 5-year disease-free survival was 67% for 30/EX vs. 88% for EX/30 ($P = 0.30$). Since there was only one patient in the 45/EX group, aeaningful analysis was precluded. This patient was alive without evidence of disease at 113 months.

Similar, although even less significant, results were seen when examining the total patient group. Compared with the 14 patients who underwent an initial excisional biopsy followed by combined-modality therapy (EX/30 plus EX/45), the 11 patients who received combined-modality therapy followed by an excisional biopsy (30/EX plus 45/EX) had a lower 5-year actuarial local control rate (70% vs. 93%, $P = 0.26$) and disease-free survival (70% vs. 86%, $P = 0.49$) but had no difference in overall survival (82% vs. 90%, $P = 0.26$). The corresponding crude rates were 73% vs. 93%, 64% vs. 86%, and 55% vs. 86%, respectively (P = NS).

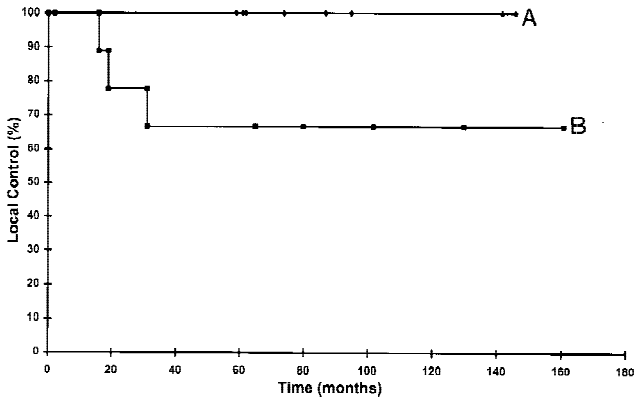

Fig. 4. Anal cancer: actuarial local control in patients undergoing combined-modality therapy with 30 Gy followed by an excisional biopsy (30/EX) (**B**) vs. initial excisional biopsy followed by 30–34 Gy (EX/30) (**A**). Wilcoxon $P = 0.08$ (NS).

Sequential vs. Concurrent Combined-Modality Therapy

Prior to 1986, patients commonly received 1 week of chemotherapy prior to starting radiation (sequential therapy) rather than chemotherapy and radiation concurrent from day 1 (concurrent therapy). Although a prior report of an unselected group of patients treated at Memorial Sloan-Kettering revealed inferior results with sequential compared with concurrent combined-modality therapy [15], in our present analysis, which is limited to the subset of patients undergoing an excisional biopsy, there were no significant differences in local control or survival between these two approaches. For the total patient group, the 5-year actuarial local control for sequential vs. concurrent treatment was 77% vs. 91% ($P = 0.51$). The crude rates were 79% (11/14) and 91% (10/11), respectively. The 5-year overall survival rates were 86% for sequential therapy and 86% for concurrent therapy ($P = 0.58$). The crude overall survival rates were 57% and 82%, respectively (P = NS).

Margin Status

Of the four patients with microscopic positive margins, one patient in the EX/45 group developed local failure at 15 months. He was successfully salvaged with an abdominoperineal resection. The other three remain without evidence of disease.

Patterns of Failure

Four of 25 patients (16%) developed local failure at 14–31 months. Of these four, one had synchronous local plus distant failure and one developed metachronous distant failure 86 months following a local failure. One patient presented as a inguinal lymph node failure. This patient had positive inguinal nodes at diagnosis, which recurred 8 months following combined-modality therapy. This patient was salvaged with an inguinal lymph node dissection and additional inguinal node radiation. One patient presented with only distant metastasis at 64 months and is dead of disease.

Sphincter Function

A total of 14 patients were eligible for sphincter function analysis. The remaining 11 patients were excluded for the following reasons: five, dead of cancer or intercurrent disease; three, lost to follow-up; and three, salvage abdominoperineal resection. Of the 14 eligible patients, 1 (7%) had excellent, 10 (71%) had good, 2 (14%) had fair, and 1 (7%) had poor function. Therefore, 11 (79%) had good to excellent sphincter function. The 5-year actuarial frequency of good to excellent sphincter function was 92%.

DISCUSSION

Combined-modality therapy is the standard of care for patients with invasive anal canal cancer [16]. A 1993 National Cancer Data Base survey of 1,289 patients reported that only 20% of patients with anal cancer were managed with surgery alone [3]. Combined-modality therapy either alone or combined with surgery was used in 63% of cases.

In some patients, the primary tumor has been removed by an excisional biopsy. Often, anal masses thought initially to be benign hemorrhoids or polyps are excised and are found incidentally to be carcinoma. Also, if anal carcinoma is suspected and the lesion is small, a diagnostic local excision may be performed. The question arises as to how to optimally manage these patients with subsequent combined-modality therapy. Since there is no gross disease, do such patients require full doses of radiation (45 Gy) or are lower doses acceptable? Since one of the determinants of the toxicity of pelvic radiation is the radiation dose, it would be helpful to deliver the lowest dose without compromising the therapeutic result.

For small anal canal cancers, some investigators advocate an excisional biopsy alone as a treatment option. Although one study from the Mayo Clinic reported a 5-year local control of 92% (12/13) with an excisional biopsy alone, other series reveal a higher local recurrence rate. Longo et al.[17] reported a local failure rate of 62% (8/13) of stage I–III patients undergoing an excisional biopsy alone. All patients with stage II (3/3) and stage III (1/1) recurred locally. Other series reveal a local recurrence rate, depending on stage, of 33%–91% of patients treated by an excisional biopsy alone [2,18–21].

In contrast, higher rates of local control have been demonstrated in patients treated with an excisional biopsy followed by radiation therapy. In a series from the M.D. Anderson Cancer Center, nine patients with stages I–II anal canal cancer were treated with an excisional biopsy followed by a median dose of 53.5 Gy [22]. Six underwent an Ir-192 implant alone or as part of their

radiation treatment. All were locally controlled. Dobrowsky et al. [7] reported 86% local control in seven patients with stages I–III disease who were treated to a median dose of 60 Gy after an excisional biopsy. A similar local control rate (92%) was reported by Martenson et al. [23] in 13 patients treated with an excisional biopsy followed by 55–67 Gy.

Although radiation alone has been shown to be effective in controlling anal cancer, higher doses are required compared with combined-modality therapy [24,25]. Improved colostomy-free and disease-free survival rates have been reported with combined-modality therapy compared with radiation alone in phase II trials from the Princess Margaret Hospital and a phase III randomized trial from the European Organization for the Research and Treatment of Cancer (EORTC) [24,26]. Therefore, combined-modality therapy is the preferred treatment.

The largest modern series of patients treated by local excision was reported by Longo et al. [17]. Of 164 patients who underwent a local excision, 109 received postoperative combined-modality therapy (median dose, 4,200 cGy with or without a 5.4-Gy boost). The majority received 5-FU plus mitomycin-C.

The overall local control rate was 79%. Local control by stage included stage I, 90% (53/59); stage II, 59% (22/37); and stage III, 100% (6/6). A dose-response relationship of radiation dose and local control was not seen. Multivariate logistic regression analysis revealed that tumor stage and the method of treatment were prognostic factors for local control. The radiation dose and duration of therapy were not found to be prognostic factors.

Some series suggest that when larger primary tumors are treated with combined-modality therapy, they require higher doses of radiation. Sischy et al. [27] reported an RTOG study of 79 patients in which 40.8 Gy in 5 weeks was effective in locally controlling tumors <3 cm (84% 2-year local control), but less effective in those tumors $\geqslant$ 3 cm (53% 2-year local control). Data from Cummings et al. [6,24,28] suggest that 45 Gy or higher is needed to optimally control tumors $\geqslant$ 4 cm.

A number of retrospective series suggest that doses of only 30 Gy when combined with concurrent 5-FU and mitomycin-C was effective in controlling the primary tumor in the majority of cases [29]. In a study from Nigro et al. [8] of 104 patients, 85 of whom had tumors $\geqslant$ 5 cm, 97 had no evidence of gross disease following combined-modality therapy. Of the 104, 31 underwent an abdominoperineal resection after combined-modality therapy because of either a treatment policy or due to gross residual disease, 62 had a local excision to evaluate for microscopic residual disease, and 11 had no further treatment.

Of the 31 patients who underwent an abdominoperineal resection, 22 (71%) had a pathologic complete response. Likewise, 61 of the 62 local excision specimens (98%) revealed no evidence of tumor. For the total patient group, 13 patients (10 of whom were treated with an abdominoperineal resection) were dead of disease; 11 of these 13 patients had tumors $\geqslant$ 5 cm or positive inguinal lymph nodes. Of the 62 who underwent local excision, 7 developed a local recurrence and 4 were successfully salvaged with an abdominoperineal resection. Of the 11 patients who were treated with combined-modality therapy alone, 9 had no evidence of disease at 2–9-year follow-up.

Our data suggest that patients with invasive anal canal cancer treated with an initial excisional biopsy followed by combined-modality therapy have equivalent local control, disease-free survival, and overall survival with doses of either 30–34 or 45–50.4 Gy. Moreover, the sequencing of the excisional biopsy with combined-modality therapy appears to be important. Patients treated with an initial excisional biopsy followed by combined-modality therapy with 30–34 Gy have better local control compared to patients treated conversely.

Patients who are treated with initial combined-modality therapy followed by an excisional biopsy may have less favorable local control. One possible explanation may be in part due to inadequate definition of the surgical tumor bed. This is supported by the results of Nigro's study [8] where 7 of the 62 patients treated with initial combined-modality therapy followed by an excisional biopsy developed local recurrence despite the finding of residual tumor in only 1 of the 62 excised specimens. However, it must be emphasized that there are other possible explanations such as bias due to the small number of patients.

Although there is justification for limiting the radiation dose to 30 Gy in patients receiving combined-modality therapy following an excisional biopsy, there may be a reluctance to deviate from the present standard of 45 Gy. Carcinomas in other anatomic sites such as head and neck, esophagus, gynecologic, and lung cancers are not adequately controlled using combined-modality therapy with 30 Gy. Aside from Nigro's study [8], there is little experience with this lower radiation dose. Although most of the present studies use 45 Gy and the phase I/II trials from the RTOG [30] and the Eastern Cooperative Oncology Group (ECOG) [31] use doses up to 59.4 Gy, it should be emphasized that gross rather than microscopic disease is being treated in these trials since the primary tumor was not removed by an excisional biopsy.

Although patients in the two subgroups were balanced with respect to stage, tumor size, and time of follow-up, it should be noted that our study was not randomized. Therefore, the differences in the results may be related to other factors such as patient selection for an excisional biopsy (diagnostic vs. therapeutic) as well as differences

in other clinicopathologic variables. Since these factors cannot be controlled for, the data should be interpreted with caution. Furthermore, given that the numbers of patients in each group were small and the retrospective nature of the analysis, it is difficult to make definitive conclusions regarding a dose-response relationship.

Likewise, the study population spanned 15 years, therefore the data are also subject to type II statistical error in which significantly different outcomes between treatment groups may be missed as well as bias due to evolving treatment policies. However, the factors such as the lower radiation doses delivered, the sequencing of treatment which, at the time, seemed appropriate, the uncommon use of an excisional biopsy in definitive management of anal cancer, and the small number of cases diagnosed each year, make it unlikely that a larger experience with such patients with long-term follow-up will be accrued.

In conclusion, our data suggest that in patients who are selected to undergo an initial excisional biopsy and postoperative combined-modality therapy, 30 Gy to the pelvis may be an adequate radiation dose. Due to the limited number of patients diagnosed each year and with only 20% undergoing an excisional biopsy, randomized control studies to evaluate 30 Gy compared to 45 Gy are unlikely to be possible.

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